Proceedings of the E-CAP' 05, European Computing and Philosophy Conference, Västeras, Sweden, June 2-4, 2005. To appear in Cambridge University Press.

THE INFORMATIONAL ARCHITECTURES OF BIOLOGICAL COMPLEXITY

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ABSTRACT

This work attempts a consistent approach to the informational organization of biological complexity. By starting out from the conceptualization of molecular recognition phenomena, an elementary panorama on the 'informational architectures' of living cells and the evolution of biological complexity may be obtained. The different modalities of molecular recognition basically revolve around 'sequential' versus 'amorphous' (or dilute) architecture. Biomolecular automata (enzymes and proteins) are the central components of the former, while DNA and RNA aperiodic sequences and whole territories constitute the latter. Starting with enzymes and proteins, if they are considered within their whole molecular environment or 'embodiment', an enlarged conceptualization of their function seems necessary. In the sequential architecture, a very complex grammar of transcription and translation processes is extended upon a plurality of molecular territories: base, codon, promoter, operator, intron, exon, split gene, gene territory, centromere, telomere, chromosome, etc. In the functional encounter of the two informational architectures, the cell cycle appears as the global instance of reference, up to the point of envisioning the cellular construction of 'meaning' throughout the agency of dedicated networks of molecular automata (basically belonging to the Cellular Signaling system) that are impinging on DNA sequences. Subsequently, a crucial difference in the evolutionary problem-solving strategies of prokaryotic and eukaryotic cells would be based on their very different DNA grammar. Their respective universality in evolutionary problem solving is addressed in one case directly towards the solution of molecular 'recognition' phenomena, while in the other case is addressed towards harnessing molecular 'organization' phenomena (morphology and differentiation). The peculiar handling of DNA sequences by eukaryotes suggests a parallel with the von Neumann scheme of modern computers, including the cellular capability to "rewrite the DNA rules" along ontogenic development.

Keywords: Molecular recognition, Informational architectures, Molecular automata, DNA grammar, Embodiment of functional agents, von Neumann scheme, Rewriting automata.

1. INTRODUCTION: MOLECULAR RECOGNITION AS A KEY TO BIOLOGICAL INFORMATION AND BIOLOGICAL COMPLEXITY

Information and complexity are amongst the most vexed terms in theoretical biology and related disciplines. Conversely to top-down approaches which start out from preconceived notions of what are the most relevant informational aspects of the living cell, the approach followed here will be based on a bottom-up strategy, directly linking informational structures with molecular recognition modalities (Conrad, 1996; Marijuán, 2003).

Molecular *specificity*, together with *affinity*, provides the ground for all molecular recognition phenomena. These two terms are essential concepts of molecular sciences, and of classical chemistry: all chemical reactions are based on the specificity of the intervening molecular partners, which at the same time are endowed with an inherent affinity or (free energy) reaction capability. By far, it is in the myriad of heterogeneous molecules that constitute living matter where this phenomenon of molecular recognition reaches its maximal ubiquity, universality, and combinatory capabilities.

An initial image may be illustrative ("worth's one thousand words"): see Fig. 1. What's happening there? The drawing symbolically represents the encounter of two fundamental avenues of biological organization: eukaryotes vs. prokaryotes (actually, a lymphocyte is engulfing a coli bacterium). How many molecular recognition encounters may be distinguished there? In both cellular systems, thousands of specific molecular encounters are taking place in an organized way (Goodsell, 2004), and apparently their mechanistic matching occurs beyond any useful taxonomy. However, this may not be the case, as we will argue soon.

Figure 1. A lymphocyte engulfing a coli bacterium (from Goodsell, 1991, 2003, modified).

At the same time, in these two cells which symbolize the two main avenues of biological complexity, we may distinguish between the shallow or *extensive computation* performed by microbial communities and the intensive or *deep computation* characteristic of

eukaryotic multicellularity –-with the caveat that we are superficially equating 'computation' with evolutionary problem-solving. For a variety of organizational-combinatoric reasons, only eukaryotic cells have been able to organize a deep evolutionary exploration of multicellularity, assembling together the complexity of both morphology and differentiation processes. While prokaryotic cells have organized vast multi-species communities with extensive horizontal gene transfer, they have not gone very deep in the exploration of multicellular colonies endowed with stable morphologies and permanent tissue differentiation. Prokaryots are missing a fundamental combinatoric step in their DNA grammars, as we will argue in the following sections.

1.1. LOOKING FOR A UNITARY INFORMATIONAL BACKGROUND

Returning to the question of how many specific recognition encounters could be distinguished within the biomolecular 'soup' of any living cell (Goodsell, 1991), it is surprising that in spite of the ubiquity and universality of molecular recognition phenomena, they are not well focused in their biomolecular generality yet.

Molecular recognition is like any other specific chemical reaction; it simply implies the "making and breaking of bonds". The problem is that biomolecular instances involve an amazing variety of bond types and combinations of Coulombian motifs, that together provide specificity and affinity to the whole intermolecular encounters (covalent bonds, hydrogen bonds, hydrophobic / hydrophilic forces, dipole forces, van der Waals forces, Coulombian forces, etc.). Dozens or even hundreds of weak bonds may participate, for instance, in the formation of a protein-protein specific complex. Quite probably, measuring molecular recognition and establishing its crucial parameters can only be realized biologically on a case-by-case basis. At least this is the current trend in most molecular biological and molecular dynamic approaches.

A few references, however, could provide some interesting insights on molecular-recognition generalities. First, W. Meggs (1998) about "biological homing", contemplated particularly from a Coulombian "lock and key" combinatoric point of view; then S.K. Lin (2001) about the thermodynamic entropy and entropy of mixing changes derived from molecular similarity changes; and finally M. Carlton (2002), with proposals for measuring the information content of any complex molecular system.

1.2. SYMMETRY CONSIDERATIONS

The usefulness and depth of symmetry considerations in molecular recognition phenomena, as emphasized by Lin (2001), are self-evident. Symmetry allows an immediate classification of biomolecular recognition occurrences by means of three ordering categories: *identity, complementarity,* and *supplementarity.* They respectively mean: recognition by sharing identical molecular properties (e.g., self-organization of phospholipids in membranes), recognition by means of complementary properties of the molecular partners (e.g., nucleic acids' double helix), and recognition through a quasi-universal capability to envelop any molecular shape by building a complex molecular scaffold of bonds around the target (e.g., enzymic active sites, protein complexes).

From an organizational point of view, these very categories based on symmetry considerations seem to be reflecting the global distribution of molecular functions within the cell: identity in the structural self-organization of membrane and cytoskeleton systems,

complementarity in the informational memory-banks of nucleic acids, and supplementarity in the active sites and recognition-surfaces of enzymic molecular machinery. See Fig. 2.

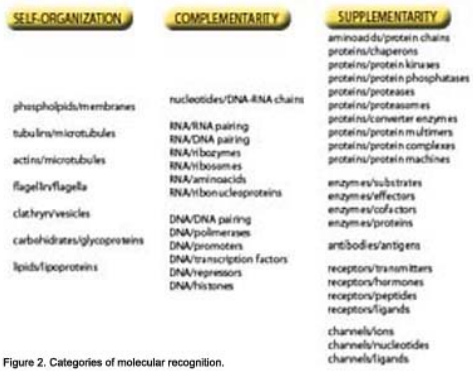

Figure 2. Categories of molecular recognition.

In the living cell, the most important functional interrelationship concerns the population of biomolecular agents (automata), which are cellularly built by means of transcriptional and translational processes performed after the codes established in the sequential arrangement of nucleic acids. This amazing correspondence between individual amino acids integrated in molecular machines and sequences of triplets in structural banks of 'DNA memory' –-the arch famous *genetic code*-- may be in itself subject of further symmetry considerations (Petoukhov, 1999; Marijuán, 2002). The code essentially represents the foundations of biological evolvability. By tinkering at multiple levels upon DNA sequences, living cells can substantially change the populations of molecular agents and subsequently alter any organismic performances (Lima de Faria, 1988, 1995).

The coding relationship between DNA sequences and proteinaceous agents is also integrated within the multiple levels of DNA metabolism (the "fluid genome" views). Thereafter, the astonishing complexity of the grammar superimposed onto the DNA/RNA encoding (which involves a plurality of molecular territories: base, codon, promoter, operator, intron, exon, split gene, gene territory, centromere, telomere, chromosome, etc.), and which is remarkably higher in eukaryotes, becomes congruent with the multifarious engines of change in nature's genetic algorithms. In evolutionary terms, the generation of variety within biological genetic algorithms becomes surprisingly complex in most eukaryotic genomes: SNPs, repetitive DNA, mobile elements, transposons, retrotransposons, telomere shortening, gene and segmental duplications, chromosome fissions and fusions, whole genome duplications, symbiosis, etc. The striking complexity of eukaryotic beauplans and organismic physiologies has been achieved only by the combined action of all those engines of variation.

2. MOLECULAR AUTOMATA: THE ENZYMIC WORK CYCLE

Enzymes and proteins, the agential stuff coded onto the DNA, appear as flexi-molecular machines with a life cycle of their own (Ho, 1995). Their constitutive structure of amino acids is permanently caught into a state of flow, from birth at ribosomes to final degradation at proteasomes. Actually, it is in the enigmatic folding process taking place at chaperons (in itself a computational NP-problem) where enzymes and proteins acquire

their machine-like characteristics, which enable them to perform a regular function within the cell.

Enzyme (and protein) function is but a continuation of the folding process. Apparently it implies a clear and regular succession of enzymic states: specific molecular recognition of the substrate, mutual coupling, lowering of the activation energy, interconversion between forms of energy, exit of the substrate transformed into product, and culmination of a regular work cycle (Marijuán and Westley, 1992; Urry, 1995). In fact, classical biochemical approaches have described this regular functioning through deterministic rate equations, non-linear ones which are often analyzed in a linear simplified way by means of control theory.

Nevertheless, this functioning may also be approached probabilistically. A stochastic dynamics –*molecular automata*– where enzymes 'fire' their state transitions according to probabilities derived from the free energy differences in between states, can be more realistic than classical equations of control theory (Marijuán, 1994). Moreover, such probabilistic dynamics would be closer to the stochastic nature of transitions in the 'post-folding' energy landscape from which the different states of the enzyme cycle are derived (Frauenfelder et al., 1991; Shimizu and Bray, 2001). The correspondence between the enzyme's chemical graph and the automata table of states is illustrated in Figure 3.

States		Inputs								Outputs	
Previous	Next	a	b	a*	k_{-1}	k_{-2}	k_3	k_{-3}	k_4	a	a*
I	I	/	0	/	/	/	/	/	/	0	0
I	A	/	1	/	/	/	/	/	/	0	0
A	I	0	/	0	1	/	/	/	/	0	0
A	A	0	/	0	0	/	/	/	/	0	0
A	X	1	/	0	0	/	/	/	/	0	0
A	T	0	/	1	0	/	/	/	/	0	0
X	A	/	/	/	/	1	0	/	/	1	0
X	T	/	/	/	/	0	1	/	/	0	0
X	X	/	/	/	/	0	0	/	/	0	0
T	A	/	/	/	/	/	/	0	1	0	1
T	X	/	/	/	/	/	/	1	0	0	0
T	T	/	/	/	/	/	/	0	0	0	0

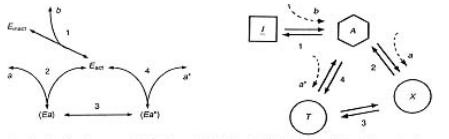

Figure 3. (Left) Formal mechanism of an isomerase bisustrate regulated by the activator b. The bisustrats and the product are a and a*. (Right) Qualitative representation of the enzyme's action. The states I, A and T correspond with Einact, Eact and Ea*. The 1 and 0 values represent the occurrence or non-occurrnce of the specific phenomenon associated to each variable (e.g., binding of sustances, spontaneus dissociation). The sign"/" means that the value of that particular variable is indifferent for thr state transition considered. ()

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2.1. ENZYME NETWORKS

Enzymes and proteins do not act in isolation. By sharing their inputs and outputs, by having multiple interconnections through effectors (either activators or inhibitors), and by directly acting upon each other (e.g., protein kinases, proteases), and also by means of the formation of complexes, they are actually caught into enormous protein networks. The new *in vivo* approaches, derived from genomic and proteomic analysis, and from signaling science and other 'omic' fields, have dramatically changed the classical views about *in vitro* (mostly metabolic) enzyme networks (Kitano, 2001; Ravasz et al., 2002).

In fact, enzyme and protein circuits are displaying any conceivable class of functional interrelationship: positive and negative feedback, amplification cascades, feedforward, lineal and parallel processing, robustness and resilience properties, sensitivity, redundancy, graceful degradation, variable interconnection, etc. (Hartwell et al., 1999). At a global scale, *power laws* clearly emerge in the functional connectedness between enzymes, and also in the formation of protein complexes (Maslov and Sneppen, 2002). This lawfulness seems to

be derived from the very formative processes at work in the evolution of genomes (related to “fluid genome” views).

2.2. EMBODIMENT OF FUNCTIONAL AGENTS

Apart from discussing the stochasticity of the individual enzyme and protein functions, we have to pay attention to the global role of *embodiment* in the way such functionality is deployed intracellularly. For instance, the organization of degradation processes or *degradomics* (traditionally forgotten) nowadays appear almost as complex as the transcription process itself (Marijuán, 1996, 2002).

In fact, definitions of biomolecular function have to pay attention not only to the functional *‘what’* dictated in the active site of the enzyme, but also to a series of accompanying processes distributed over different parts of the molecular structure, which may include: modulation by effectors, intracellular transportation, permanent (post-translational) modification, formation of complexes, the time-frames derived from transcription and translation, and finally degradation. So the *‘what’* of the functional clause should be accompanied by circumstances such as *‘how fast’, ‘where’, ‘which way’, ‘with whom’, ‘when’,* and *‘how long’*.

In general, the functionalities of the active site and of the retinue of accompanying processes are independently defined onto the DNA sequences, constituting *addresses* which, as said, are separately coding for function (‘primary address’ coding the active site), and for control, transportation, splicing, modification, complexes, transcription-translation, degradation, etc. (each one implying some specific ‘secondary addresses’ in the DNA coding, irrespective that they may be functionally operative in the DNA, RNA, or in the protein stages).

In prokaryotes, the global embodiment processes are far simpler than in eukaryotes –-in correspondence, their protein components are smaller and contain fewer domains comparatively. As a matter of fact, the possibility of systematic tinkering upon multiple modules and domains materializes as the distinctive evolutionary strategy of eukaryotes, the tool-box of their multicellularity. A serial-combinatoric arrangement of exons and introns (which usually constitute folding domains), tissularly tailored by differential splicing, allows eukaryotes a far bigger proteome than prokaryotes (around one or two orders of magnitude) without multiplying the number of genes involved (Claverie, 2001).

By tinkering and playing combinatoric games upon exons and introns containing a vast array of secondary addresses, eukaryotic cells may systematically explore and change the whole boundary conditions surrounding the triggering of each biomolecular function -- mastering all those circumstances of *when, where, how fast, which way, for how long, with whom,* etc., which together co-determine the functional action of any eukaryotic enzyme or protein (Marijuán, 2003).

3. INTEGRATED FUNCTIONING OF THE CELL: THE CELL CYCLE

The emergence of regulated cell cycles appears as a necessary evolutionary accomplishment. Out from vast enzyme networks and protein complexes, each one individually having a stochastic function, there emerges a regularized cell-cycle of quasi-deterministic characteristics capable of performing a specialized function. The cell cycle

becomes a *macro-engine* (elegantly driven by protein degradation), the accurate control of which constituted an evolutionary prerequisite for the onset of multicellularity. See Fig. 4.

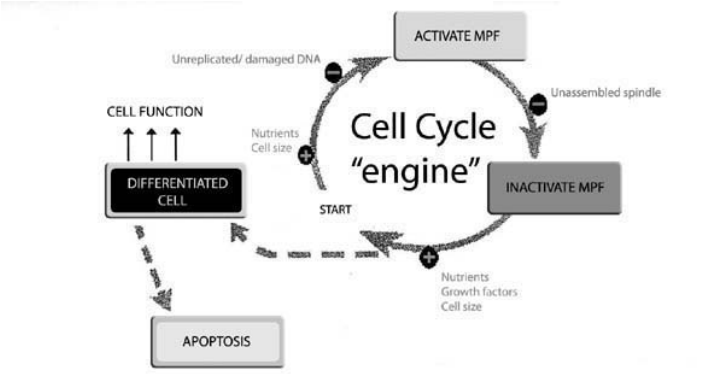

Fig.4. Cell-cycle engine and its regulation. The MPF (maturing promoting factor) is composed of cyclins and associated kinases. Cyclins, fundamental control elements, are degraded throughout the cycle in a ubiquitin-dependent process. Other proteins such as p21, p16, p27 and p53 participate in the control structures known as checkpoints. Every checkpoint instantiates a signal transduction system in its own. They receive a plurality of signals, integrate them, and transmit the results to other regulatory components. The transit towards a differenciates cell type implies a permanent interruption of the cycle in one checkpoint (the cell becomes committed to develop its specialized function). Apoptosis occur due to senescence or to the arrival of specific signals.

How can the cell cycle be so exactly and quasi-deterministically produced out from individual stochastic components? Recent work on proteomic networks is throwing a new light on the biomolecular mechanistic scheme of the cell cycle adumbrated in the 80's and 90's (MPF, cyclins, CD protein kinases, checkpoints, etc.). There seem to be different kinds of *hubs* in the proteomic nets, both transient and permanent ones, which collectively drive the evolution of the whole system of networks, subnetworks, circuits, complexes, etc. towards common attractors. Ironically, individual stochasticity becomes a must for achieving a viable whole, as was already claimed by some molecular biologists out from experimental grounds –-Misteli (2001).

Overall, the living cell is functioning as a tireless synthesizer, always filling-in its functional needs of active elements by means of (signaled) protein synthesis, coupled with massive protein degradation. Therefore, as much as the living cell is always in the making, in a continuous self-production process, it is simultaneously engaged in its own degradation, adaptively getting rid of its unnecessary, obsolete, or disturbing functional elements (Marijuán, 1996).

Adaptively weaving and un-weaving the own structures becomes a highly complex *calculus* to be performed by any cell belonging to a multicellular organism. It implies filling-in the own functional needs following internal and external signals, and keeping a balance between synthesis and degradation processes. How to select, thus, among the multiple pathways of *control* and intervention that are possible? And how to orchestrate them just in time, adaptively? For evolutionary reasons, a global economy of action has to be involved (Conrad, 1996; Marijuán, 1996).

3.1. SIGNALING SYSTEMS

The Cellular Signaling System appears as the computing apparatus evolved to confront the adaptive control challenge. Out from prokaryotic origins, the CSS of eukaryotes --or *signalome*-- integrates the communication events with the synthesis and degradation

needs. It comprises hundreds of different classes of dedicated molecular agents (receptors, ion channels, transducers, amplification cascades, second messengers, intermediate effectors, final effectors) that have been arranged differently in each tissue. See Fig. 5. Every cell-type has tailored its specialized signalome along its developmental trajectory, in dependence of its own history of received signals and self-modifying processes (Marijuán, 2002).

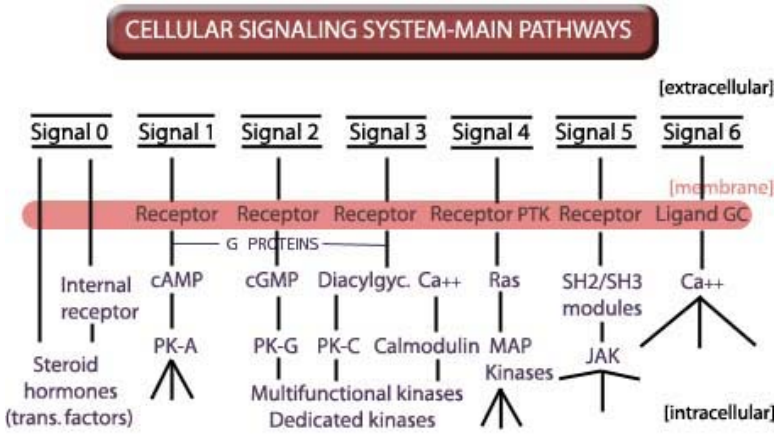

Fig.5. Principal signaling pathways that operate in eukaryotic cells.The signaling paths on the left (steroids) are usually associated with cell fate and hormonal effects. The paths mediated by G proteins (1, 2, 3) have greater amplification in order that are ideal for sensory receptors. Paths 4 and 5 represents the acces for neuropeptide accion. Path 6 (ligand-gated channels) is the cortical path for glutamate and GABA neurotransmitters. *[This representation does not include the intermediate effectors between receptors and second messengers, nor the networking of paths, nor the counteracting phosphatases]

The general “detection, measurement, and intervention” character of CSS has to be emphasized. The second messengers (cAMP, cGMP, Ca, InsP3, diacylglicerol, ceramide...) are dramatically modified in their concentrations by the different signaling paths that have been transiently activated, within a generalized cross-talking among all activated paths —echoing McLuhan, in the cellular system “the pathway is the message.” Therefore, particularly throughout the second messenger concentrations, an integrated perspective (measurement) of the different internal and external influences at play is obtained within the cell, and is subsequently passed towards intermediate chains and the final effectors. At one of the crucial ends of the signaling command-chain, the nuclear machinery is waiting to be fed with a combination of *ad hoc* signals in order to change the transcriptional status of the genome.

The nuclear part of the whole signalome apparatus has already been implementing the *histone code,* in order to allow a tight grip upon the euchromatin-heterochromatin states which regulate access to transcription -–so that the well measured signals from the cytoplasmic signalome may be finally enacted as a new transcription program in relation with the advancement of the cell cycle or with the specialized function of the cell.

3.2. CONVERGENGE ON THE CELL CYCLE

Everything has to converge factually on the cell cycle: metabolism, signaling system, protein synthesis, protein degradation, network organization, and control of the cell cycle itself (Marijuán, 1996).

Cellular “checkpoints” are instances of overall convergence where the fusion of a plurality of processes may be gauged. They are usually implemented as protein complexes where the ongoing transformation processes related to cell-division, signaling, metabolism, etc. may talk to each other and produce a unitary signal of advancement along the phases of the cell cycle --or they may discard any further advancements, and cell death ensues, either by apoptosis or by necrosis. Checkpoints act as *decision points* in between the well known four phases or stages of the eukaryotic cell-cycle: G1, S, G2, and M. Symbolically, a noticeable degree of stochasticity reappears within most of these decision loci, as several highly complex molecular operations are simultaneously launched, particularly during the S and M phases, and different signaling balances and metabolic and environmental constraints have to be rigorously maintained within the “intercellular milieu.” The cells that fail to cross the whole checkpoints are doomed to an apoptotic fate; otherwise global deregulation of their cell cycles would ensue.

As successive rounds of replication are accomplished, there occurs a functional rewriting of ‘DNA rules’. The transcriptional status of most DNA regions is systematically altered as the cell advances along the totipotent, pluripotent and stem cell path, until completion of the tissular differentiation and specialization is achieved (Gasser, 2002). The euchromatine / heterochromatine state of a number of genomic regions is irreversibly altered by signaled implementation of the “histone code”. See Fig. 6. From the point of view of formal systems, this unusual characteristic of “rewriting the own rules” could be significant concerning the cellular automata field (Wolfram, 2002), perhaps opening new paths towards new types of biologically inspired cellular automata capable of negotiating complex morphological / differentiation spaces.

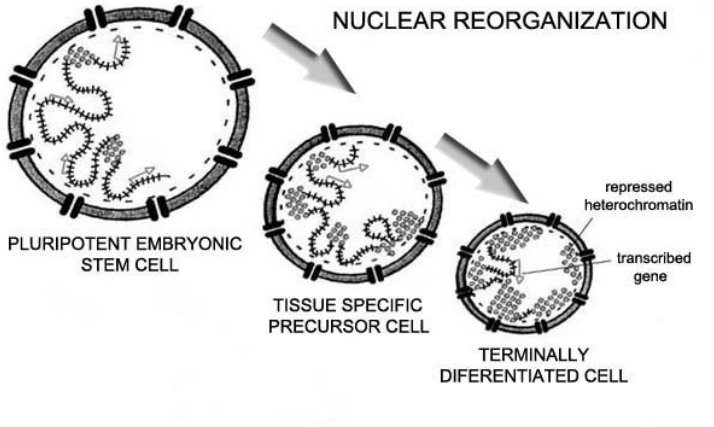

Figure 6. Rewriting the DNA rules. The model predicts that progressive differentiation within a multicellular organism cell will restrict both the expression profile and the dynamics of the cell's interphase chromatin, modifying the gene potential to be either transcribed or into an inactive state. (after Gasser, 2002, modified)

The cell cycle may be an appropriate stage to discuss the intracellular construction of meaning too. Any signal of external (or internal) origins will convey the *meaning* generated by its perturbation trajectory across the CSS and associated checkpoints, with *ad hoc* synthesis & degradation of proteins included. Complete irrelevance when the signal is dissipated into the sea of equifinal trajectories within the phases of the cell cycle. Utmost relevance when the signal itself determines passage across an interphase checkpoint. And functional meaningfulness when the signal triggers realization of the specialized cell-function. In any case, the abstract construct of the cell cycle becomes the necessary reference. Properly speaking, living matter does not refer to *states*, but to *phases* established along the advancement of a life cycle.

With the spiraling and multiplication of multicellular cycles along the eukaryotic developmental path, the hallmark for a new type of biocomplexity is set. The prokaryotic cell cycle has been projected to a formidable complexity height in multicellular eukaryotes, setting the stage for a number of *emergences* discussed in computational and philosophical fields: transition from stochasticity to systemic robustness and quasi-determinism, establishment of top-down causality, autonomy, agency, plus the special appearance of quasi-universal information processing systems (advanced Central Nervous Systems), not to speak about the evolutionary origins of consciousness and its neuronal and biomolecular basis.

4. CONCLUDING COMMENTS: ON EVOLUTIONARY PROBLEM-SOLVING STRATEGIES (& A PHYSIOLOGICAL CODA)

In the extent to which the complexity growth of eukaryotes has been built by tinkering upon the scheme of *functional addresses* and *secondary addresses* put together onto the same DNA memory, the parallel with the von Neumann scheme of modern computers seems unavoidable –in computers, logical functions and memory addresses are also put together in the CPU memory.

Because of this DNA scheme, the evolutionary genetic algorithms for physiological problem-solving are largely parallelized in eukaryotes. The different components of the biomolecular solutions may be tinkered with separately, and linked together later on. Besides, every molecular stage (transcription, folding, transportation, modification, complexes, degradation), specifically coded onto DNA addresses, may be used as a new functional element of control. Solutions may be chosen, then, from an augmented molecular set.

The so called “Central Dogma” of classical molecular biology should not be taken cellularly as a closed black-box; rather its successive stages could participate as legitimate molecular partners, each one endowed with endogenous recognition capabilities, within a whole *transmolecular matrix* of controlling interactions (Marijuán, 2002, 2003). See Fig. 7. As an instance, in the recently discovered phenomenon of RNA interference, scores of micro RNAs are transcribed for the only purpose of using up their molecular recognition capabilities within the context of other DNA transcription and RNA translation events, collectively known as “gene silencing.”

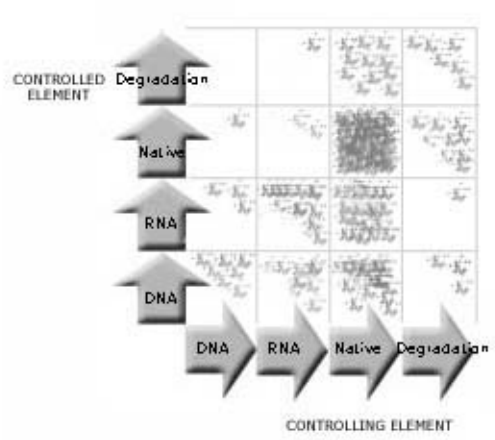

Figure 7. Transmolecular Matrix of controlling interactions.

Concerning the evo-devo discussions (Raff, 1996; Carroll, 2001), the explorations of connectivity and functional modules in multicellular eukaryotes become far easier along this rationale. In the transmolecular matrix regime, "functional loans" between developmental paths may be easily arranged. When conflicts arise, gene and segmental duplications may straightforwardly solve the problem.

In actuality, the evolutionary coupling between the two informational architectures of life, the sequential and the amorphous, has explored almost every conceivable beauplan and organismic physiology. Life has thrived throughout the deployment of an organization with amazing informational capabilities.

REFERENCES

Carlton M. (2002) The information paradigm. Posthumous compilation available at: http://conway.cat.org.au/~predator/paradigm.txt

Carroll, S.B. (2001) Chance and necessity: the evolution of morphological complexity and diversity. *Nature* 409 pp. 1102-1109.

Claverie J.M. (2001) What If There Are Only 30,000 Human Genes? *Science* 291pp. 1255-1257

Conrad M. (1996) Cross-scale information processing in evolution, development and intelligence. *BioSystems* 38 pp. 97-109.

Frauenfelder H., Sligar S.G. and Wolynes P.G. (1991) The Energy Landscapes and Motions of Proteins. *Science* 254 pp. 1598-1603.

García-Olivares A. and Marijuán P.C. (2004) Emergence of power laws from partitional dynamics. *BioSystems* 74, 63-71.

Gasser S.M. (2002) Visualizing Chromatin Dynamics in Interphase Nuclei. Science 296, 1412-1416.

Goodsell D.S. (1991) Inside a living cell. *TIBS* 16, 203-206.

Goodsell D.S. (2004) *Bionanotechnology: Lessons from Nature.* Wiley-Liss Inc., New Jersey.

Hartwell L.H., Hopfield J.J., Leibler S. and Murray A.W. (1999) From molecular to modular cell biology. *Nature* 402 pp. C47-C52.

Ho M.V.(1995). *Bioenergetics*. The Open University, London,

Kitano H. (2001) Systems Biology: Towards System Level. In *Foundations of Systems Biology*, ed. by H. Kitano. The MIT Press, Cambridge.

Lima-de-Faria A. (1988) *Evolution without selection: Form and function by autoevolution.* Elsevier, Amsterdam.

Lima-de-Faria A. (1995) *Biological Periodicity*. JAI Press Inc., London.

Lin S.K. (2001) The Nature of the Chemical Process. 1. Symmetry Evolution –Revised Information Theory, Similarity Principle and Ugly Symmetry. *Int. J. Mol. Sci.* 2 pp. 10-39..

Marijuán P.C. (1994) Enzymes, automata and artificial cells. In *Computing with biological metaphors,* ed. by R.C. Paton. Chapman & Hall, London, pp. 50-68..

Marijuán P.C. (1996) The Cell as a Problem-solving 'Engine'. *In Computation in Cellular and Molecular Biological Systems*, ed. by R. Cuthberson, M. Holcombe and R. Paton. World Scientific, Singapore, pp. 183-194.

Marijuán P.C. (2002) Bioinformation: untangling the networks of life. *BioSystems* 64, pp. 111-118.

Marijuán P.C. (2003) From inanimate molecules to living cells: the informational scaffolding of life. In *Energy and Information Transfer in Biological Systems*, ed. by F. Musumeci, L.S. Brizhik and M.W. Ho. World Scientific, Singapore.

Marijuán P.C., Pastor J. and Villarroel M. (1999) The Language of Cells: A Compositional Approach to Cellular Communication*. Symmetry: Culture and Science*, Vol. 9, pp. 383-392.

Marijuán P.C. and Westley J. (1992) Enzymes as molecular automata: a reflection on some numerical and philosophical aspects of the hypothesis. *BioSystems* 27 97-113.

Maslov S. and Sneppen K. (2002) Specificity and Stability Topology of Protein Networks. *Science* 296, pp. 910-913.

Meggs W.J. (1998) Biological homing: hypothesis for a quantum effect that leads to the existence of life. *Medical Hypothesis* 51, pp. 503-506.

Misteli T. (2001) Protein Dynamics: Implications or nuclear Architecture and Gene Expression. *Science* 291, pp. 84-847.

Petoukhov S.V. (1999) Genetic Code and the Ancient Chinese Book of Changes*. Symmetry: Culture and Science*, Vol. 10, pp. 221-226.

Raff R.A. (1996) *The Shape of Life*. The University of Chicago Press, Chicago.

Ravasz E., Somera A.L., Mongru D.A., Oltvai Z.N. and Barabási A.L. (2002) Hierarchical Organization of modularity in Metabolic Networks. *Science* 297 pp. 1551-155.

Shimizu T.S. and Bray D. (2001) Computational Cell biology –The Stochastic Approach. In *Foundations of Systems Biology*, ed. by H. Kitano. The MIT Press, Cambridge.

Urry D.W. (1995) Elastic Biomolecular Machines. *Scientific American* January pp. 44-49.

Wolfram S. (2002) A New Kind of Science. Wolfram Media Inc.